

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
24 October 2002 (24.10.2002)

PCT

(10) International Publication Number
WO 02/083039 A1

(51) International Patent Classification⁷: A61F 2/06 (74) Agents: KERRIGAN, Cameron et al.; Squire, Sanders & Dempsey, L.L.P., 600 Hansen Way, Palo Alto, CA 94304-1043 (US).

(21) International Application Number: PCT/US02/11581 (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 12 April 2002 (12.04.2002) (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

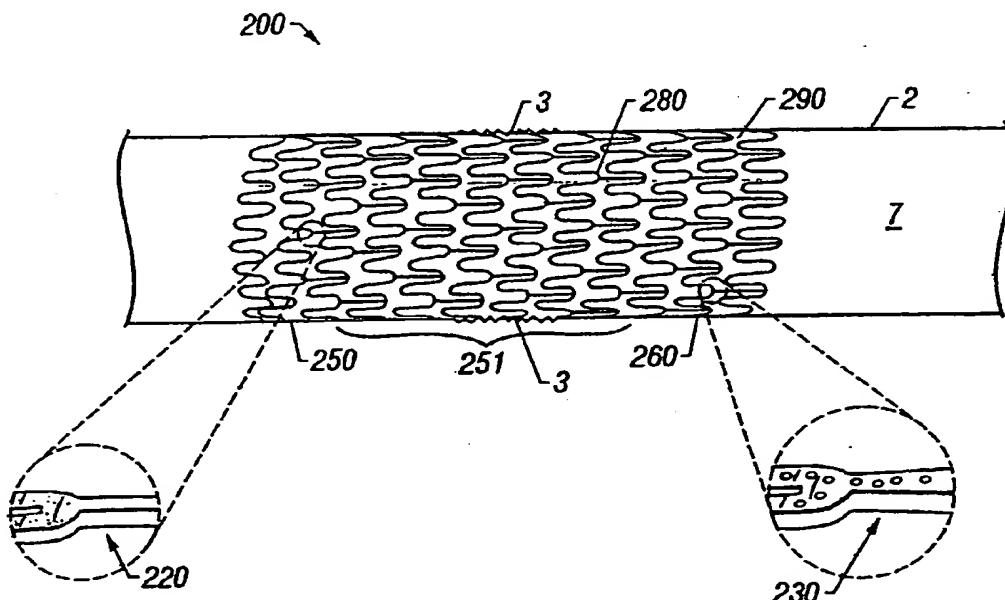
(25) Filing Language: English (30) Priority Data: 09/834,012 12 April 2001 (12.04.2001) US (31) Applicant: ADVANCED CARDIOVASCULAR SYSTEMS, INC. [US/US]; 3200 Lakeside Drive, Santa Clara, CA 95054 (US).

(32) Inventors: HOSSAINY, Syed; 34325 Tupelo Street, Fremont, CA 94555 (US). TANG, Fuh-Wei; 31760 Via Cordoba, Temecula, CA 92592 (US). CAHILL, Brian, P.; 1128 Fell Street, San Francisco, CA 94117 (US).

Published: — with international search report

[Continued on next page]

(54) Title: VARIABLE SURFACE AREA STENT



WO 02/083039 A1

(57) Abstract: A stent of variable surface area as determined by stent struts. The stent can have a variable surface area per unit length which accommodates a therapeutic agent. A patterned distribution of therapeutic agent can be provided throughout the stent. The stent can have an increased level of therapeutic agent near an end of the stent. A decreased level of therapeutic agent can be provided near an end of one embodiment of a stent. Indentations can be provided at the surface of the stent with therapeutic agent disposed therein. The stent can be cut with struts of variable thickness to provide the variable stent surface area.



- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

VARIABLE SURFACE AREA STENT

BACKGROUND OF THE INVENTION

[0001] The present invention relates to intravascular implants. In particular, the present invention relates to stent devices to deliver therapeutic agents such as radioisotopes or drugs.

BACKGROUND OF THE PRIOR ART

[0002] In the last several years, minimally invasive surgical procedures have become increasingly common. Minimally invasive procedures such as percutaneous transluminal coronary angioplasty (PTCA) are widely utilized. A PTCA procedure involves the insertion of an angioplasty balloon at the distal end of a catheter to the site of a stenotic lesion. Prior to treatment, the stenotic lesion is bulky and at least partially blocking the coronary artery at issue. Once advanced, the balloon is inflated compressing the stenosis and widening the lumen in order to allow an efficient flow of blood through the lumen.

[0003] Following PTCA and other stenotic treatment procedures, a significant number of patients may experience restenosis or other vascular blockage problems. These problems are prone to arise at the site of the former stenosis.

[0004] In order to help avoid restenosis and other similar problems, a stent may be implanted into the vessel at the site of the former stenosis with a stent delivery catheter. A stent is a tubular structure which is delivered to the site of the former stenosis or lesion and compressed against vessel walls thereat, again with a balloon. The structure of the stent promotes maintenance of an open vessel lumen. The stent can be implanted in conjunction with the angioplasty.

[0005] In addition to stent implantation, radiotherapy and drug delivery treatments have been developed and applied to the site of the former stenosis following angioplasty. Generally such treatments can aid in the healing process and significantly reduce the risk of restenosis and other similar problems.

[0006] In some cases, stent implantation may be combined with drug delivery or radiotherapy. For example, a stent may be drug loaded or radioactive. A stent with a therapeutic agent may be delivered to the physician about the stent delivery catheter (and with a removable shield if the stent is radioactive).

[0007] However, delivery of a therapeutic treatment throughout the site of the former stenosis is problematic. The level of uniformity in the delivery of a therapeutic agent to the injured area is dependent upon the particular stent configuration. For example, in the case a radioactive stent, the radioactive stent may have hot spots and cold spots of uneven levels of radioactivity. This is because the stent is made up of struts having radioactivity and window cells having no physical structure or radioactivity (or drug in the case of a drug delivery stent). Therefore, therapeutic agent throughout a particular stent configuration is dependent upon the strut and window cell distribution throughout that stent. Therefore, therapeutic variability results.

[0008] For example, in the case of a radioactive stent, if about 20 Grays (Gy) of radiation, as measured from 1 mm of tissue depth, are to be delivered to a vessel portion to be treated, a wide range of radiation delivery will actually occur. That is, due to the radioactive stent configuration, a non-uniform delivery, ranging from about 5 Gy to about 25 Gy is more likely delivered to the vessel portion to be treated. Due to limitations of the prior art a range of at least about 20 Gy will be delivered by a radioactive stent throughout the vessel portion to be treated in the given example. As a result, certain portions of the vessel will receive significantly more or significantly less

radiation than intended. Such a variability in delivery could lead to underdose failing to reduce the risk of restenosis in certain portions of the vessel, or overdose potentially causing further vascular injury to other portions of the vessel. This variability results regardless of the therapeutic agent to be delivered.

[0009] Additionally, certain therapeutic agents are delivered to avoid a phenomenon known as "edge restenosis". Edge restenosis is prone to occur near stent ends.

[0010] Even though a stent is structurally configured to maintain the patency of a vessel lumen, edge restenosis is prone to occur with the use of radioactive stents. Edge restenosis involves the formation of vascular overgrowths in vascular areas immediately adjacent radioactive stent ends, generally within about 2 mm of each radioactive stent end. Edge restenosis is a result of delivery of a sub-threshold level of radiation to the vascular areas immediately adjacent the radioactive stent ends. These vascular areas are near or within the site of the former stenosis. They include vasculature likely to be diseased, or subjected to a recent trauma such as angioplasty. When a sub-threshold level of radiation, between about 2 Grays and about 10 Grays, as measured at 1mm of tissue depth, reaches such vulnerable vascular areas, stenotic overgrowths may actually be stimulated. These overgrowths result in narrowed vessel portions near stent ends giving an appearance of a candy wrapper crimped around the ends of the stent. Thus, this effect is often referred to as the "candy wrapper" effect.

[0011] The occurrence of the candy wrapper effect is likely when a radioactive stent is used. This is because the intensity of radiation decreases as the source of the radiation, the radioactive stent, terminates at its ends leading to a drop of in radiation levels at vessel portions adjacent its ends. Thus, a sub-threshold radiation delivery is likely to occur near the radioactive stent ends.

[0012] As indicated, heretofore, the level of therapeutic uniformity or focus any particular stent has been able to deliver has been dependent upon that stent's configuration with respect to strut and window cell distribution. However, a stent structure (i.e. strut layout) which physically promotes maintenance of an open vessel lumen may be of a particular configuration which is not necessarily best suited for a more uniform delivery of a therapeutic agent. Additionally, this stent configuration may fail to avoid an unintended "candy wrapper" effect in which portions of the vessel adjacent the stent become narrowed.

SUMMARY OF THE INVENTION

[0013] An embodiment of the present invention provides a stent having a variable stent surface area per unit length. The variable stent surface area is used to accommodate a therapeutic agent.

[0014] Another embodiment of the present invention provides for a stent having an end and a variable stent surface area per unit length to accommodate a therapeutic agent. A decreased level of therapeutic agent is provided at the end.

[0015] An embodiment of the present invention provides for a stent having an end and a variable stent surface area per unit length to accommodate a therapeutic agent. An increased level of therapeutic agent is provided at the end.

[0016] In an embodiment of the invention a method of vessel treatment utilizing a stent with a variable stent surface area is provided. A therapeutic agent is disposed on the stent surface area to provide a patterned distribution of the therapeutic agent.

[0017] In another embodiment of the invention a method of stent manufacture is provided where indentations are cut into a surface of a stent. A therapeutic agent is disposed on the surface of the stent.

[0018] In another embodiment of the invention a method of stent manufacture is provided where struts of the stent are cut of increased thickness to provide a variable stent surface area. Therapeutic agent is disposed on the variable stent surface area.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Fig. 1 is a side view of an embodiment of a stent of the present invention.

[0020] Fig. 2 is a pictorial view of an embodiment of a stent of the present invention implanted within a vessel of a patient.

[0021] Fig. 3 is an enlarged view of an embodiment of a strut of the stent of Fig. 2.

[0022] Fig. 4 is an enlarged view of an embodiment of a strut of the stent of Fig. 2.

[0023] Fig. 5 is a cross sectional view of an embodiment of a strut taken along the line 5-5 of Fig. 4.

[0024] Fig. 6 is a chart depicting an embodiment of a dose delivery profile of the present invention.

[0025] Fig. 7 is a representation of an embodiment of a source profile of the invention.

[0026] Fig. 8 is a chart depicting an embodiment of a dose delivery profile of the present invention.

[0027] Fig. 9 is a representation of an embodiment of a source profile of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The following description makes reference to numerous specific details in order to provide a thorough understanding of the present invention. However, each and every specific detail need not be employed to practice the present invention. Additionally, well-known details, such as particular materials or methods, have not been described in order to avoid obscuring the present invention.

[0029] Referring to Fig. 1 an embodiment of a stent 100 of the present invention is shown. The stent 100 is formed of struts 180, which provide physical structure, and open spaces, referred to as window cells 190. The struts 180 are formed from stainless steel or other materials which are generally biocompatible. For purposes of illustration, the struts 180 shown have a cylindrical shape longitudinally. However, in alternate embodiments non-cylindrical strut 180 shapes are used. As discussed further herein the struts 180 provide a variable surface area to the stent 100.

[0030] Referring to Fig. 2 an embodiment of a stent 200 of the present invention is shown within a vessel 2 near the site of a former stenosis 3 to maintain the patency of the vessel lumen 7. The stent 200 of Fig. 2 is equipped with struts 280 which have variability in surface area, in terms of a change in surface area per unit length, as described further below. For each strut 280 portion, a surface area (γ) is provided which is given by the equation: $\gamma = 2\pi rlh_r$, where r is a radius (r) of the strut 280 portion, l is a length (l) of the strut 280 for the portion of the strut 280 being examined, and h_r is the roughness factor (h_r) of the strut 280 portion.

[0031] Referring to Figs. 3 and 4, strut types 220, 230 of Fig. 2 are shown enlarged. The radius (r) (or r_1 and r_2) and a given length (l) are shown (see also Fig. 5 showing a radius (r_2) of a cross-section of a strut). The strut surface area (γ) includes a loading surface 340. The loading surface 340 portion of the surface area (γ) is that portion of the surface area (γ), generally facing outward (i.e. toward vessel 2 as shown in Fig. 1), that accommodates therapeutic agent. As the overall surface area (γ) increases or decreases, so does the loading surface 340. Therefore, if strut surface area (γ) varies throughout a given length (l), as it does in the embodiment shown, then the dose amount for a given length (l) (i.e. the dose concentration (δ)) will vary throughout that same length (l). Given the equation: $\gamma = 2\pi rlh_r$, it can be seen that if the variables r or

h_r of the equation fluctuate in value, for the same given length (l), as is the case in the shown embodiment, then so too will the surface area (γ) of the strut type 220, 230 within the given length (l).

[0032] Referring to Figs. 2 and 3, in order to vary surface area (γ) of the stent 200, certain roughened strut 220 types are provided with a surface pattern. The roughened struts 220 are those in which the variable h_r , referred to above, has changed in value throughout a given length (l). Or, in other words, $\gamma' = 2\pi rl\Delta h_r$. For example, where an entirely smooth surface strut is provided (not shown), the roughness factor (h_r) is 1.0, having no effect on the surface area (γ) of the smooth surface strut. However, if the roughness factor (h_r) is greater than 1.0, the surface area (γ) will correspondingly increase as shown in the present embodiment. Therefore, the dose concentration (δ) of therapeutic agent deliverable to the vessel 2 is increased in corresponding portions of the strut 280 where (h_r) is greater than 1.0.

[0033] As shown in Fig. 3, an embodiment of a roughened strut 220 is provided of a given length (l). Moving from a first portion 360 of the given length (l) to a second portion 300, the roughness factor (h_r) changes as indicated by the change in roughness over that same length (l). That is, increased roughness, as indicated by the granular appearing texture of the loading surface 340, is provided near first portion 360. Alternatively, the value of the roughness factor (h_r) decreases and approaches a value of 1.0 near second portion 300 as shown by the smoother appearance of the loading surface 340 near second portion 300. Therefore, a roughened strut 220, as in the embodiment shown, provides one manner of varying surface area (γ) throughout a given length (l), and thus provides a variation in dose concentration (δ) throughout that same length (l).

[0034] Referring to Figs. 2 and 3, in order to increase the roughness factor (h_r) chemical, plasma, laser, mechanical or alternate methods of etching are used in embodiments of the invention. For example, in one embodiment the stent 200 is dry etched by sand blasting or plasma etched with argon in order to increase roughness.

[0035] Another embodiment focuses the increased roughness factor (h_r) at particular struts 280 by a lithography technique of coating the stent 200 with a protective polymer such as ethylene vinyl alcohol. The stent 200 is then selectively treated with a solvent, such as dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), or dimethyl acetamide (DMAc), in strut 280 areas to remove portions of the protective polymer. For example, in one embodiment, a stent end 250 is dipped into the solvent to remove protective polymer from portions of the struts 280 nearer the stent end 250. By removing the protective polymer, these portions of the stent 200 are susceptible to increased roughening following application of an etching process to an exterior of the stent. Thus, once the stent 200 is etched, an increased roughness factor (h_r) is present at the stent end 250. However, in an alternate embodiment increasing roughness interior of the stent 1 is avoided in order to promote a flow of blood through the stent.

[0036] The roughened strut 220 embodiment shown is viewed in light of its positioning in the stent 200. It can be seen that the roughened strut 220 is found near stent end 250. The roughened strut 220 includes a loading surface 340 which has been roughened as discussed above. The degree of roughening increases moving toward the first portion 360 (nearer the stent end 250) of the roughened strut 220. Alternatively, the loading surface 340 becomes smoother moving toward a second portion 300 (nearer the stent body 251). That is, in view of the stent 200 as a whole, additional surface area

(γ), and thus, increased radioactivity upon activation, is found near the stent end 250 due to the roughened strut 220 patterning provided.

[0037] Referring to Figs. 2 and 4, in order to vary surface area (γ) of the stent 200, certain struts 280 are formed as increased thickness struts 230. The increased thickness struts 230 are those in which the radius (r), referred to above, has changed in value throughout a given length (l). Or, in other words, $\gamma' = 2\pi\Delta rlh_r$.

[0038] As shown in Fig. 4, an embodiment of an increased thickness strut 230 is provided of a given length (l). Moving from a first strut portion 450 of the given length (l) to a second strut portion 400, we see that the radius (Δr) changes as indicated by the change in radius size from r_1 to r_2 respectively, with r_2 indicating an increased radius (i.e. Δr) from that of r_1 . Therefore, an increased thickness strut 230 provides an alternate manner of varying surface area (γ) throughout a given length (l), and thus allowing for a variable dose concentration (δ) throughout that same length (l). This pattern of surface area (γ) along the given length (l) holds true even in non-linear strut portions 425.

[0039] As shown with reference to positioning within the stent 200, the increased thickness strut 230 is shown near opposite stent end 260 of Fig. 1. As a result, increased surface area (γ) and thus, increased radioactivity upon activation, is provided near opposite stent end 260.

[0040] In a method of manufacturing the stent 200, including struts 280, the stent 200 is laser cut from, for example, a stainless steel tube. The laser cutting process is run according to an automated process to form a particular stent configuration. In order to increase or vary a radius (r) in portions of particular struts 280, the automated process is programmed to cut a strut 280 of increasing radius (r), for example, near opposite stent end 260. In this manner, an increased thickness strut 230 is provided.

[0041] Referring to Figs. 4 and 5, a cross section taken from the line 5-5 of Fig. 4 is shown as Fig. 5. In addition to a greater amount of loading surface 340 generally, the increased thickness strut 230 of Fig. 4 includes increased size indentations 435. As shown in the embodiment of Fig. 5, the increased size indentations 435 have been cut into the loading surface 340 with a laser during manufacture to provide additional loading surface 340 at the interior of the increased size indentations 435 by providing additional interior surface with the increased size indentations 435.

[0042] Each indentation may increase surface area by about threefold per unit area. Where the depth L is increased, surface area provided by the indentation is increased. Increased size indentations may have a depth L of about one half of the increased thickness strut 230 at the location of the indentation. Increased size indentations 435, have a depth L beyond about 60-80 microns, and are provided as thickness increases (as shown toward the opposite strut end 400 of Fig. 4). The increased size indentations 435 provide a volume as well as increased surface area (γ). In the embodiment shown, the indentations 435 are of a truncated cone shape. However, in other embodiments, other shapes are used. For example, in one embodiment of the invention, the indentations 435 are of a dimpled shape

[0043] Referring to all of Figs. 2-5, the surface area (γ) discussed in relation to the above embodiments is increased by the use of particular increased size indentations 435, an increased thickness strut 230, and a roughened strut 220. However, all of these features, alone and in any combination, are used in other embodiments to increase surface area (γ) in particular stent 200 portions and provide particularly configured and focused loading surfaces 340 for accommodating therapeutic agents. Once a particular stent 200 configuration of increased surface area (γ) is chosen and provided, it is activated with therapeutic agent, accommodated at the loading surface 340.

[0044] In an embodiment of the invention, where the therapeutic agent to be provided includes radioactive isotopes, plasma ion implantation of the isotopes into the loading surface 340 is used for activation. Embodiments of the invention employ Plasma and Ion Beam Assisted Deposition for loading. Plasma ion implantation results in radioactive ions being implanted below the loading surface 340 of the stent 200. By implanting ions below the loading surface 340, a radioactive layer is formed which is shielded from a biological environment when the stent 200 is later inserted into a patient. Plasma ion implantation involves loading the stent 200 into an isolation chamber where a plasma of radioactive ions is generated. The plasma is provided by providing a liquid or gas which includes a stable precursor to the ion type to be used. Radio Frequency (RF) or microwave power are coupled to the isolation chamber to transform the mixture into a plasma state within the chamber. Negative voltage energy pulses are then applied to the treatment stent 1 to cause implantation of ions below the loading surface 40. In various embodiments, ions such as Phosphorous (P^{32}), Rhenium (Re^{188}), Yttrium (Y^{90}), Palladium (Pd^{103}), Iodine (I^{125}), and Ruthenium (Ru^{106}) are loaded above and below the loading surface 340 in this manner.

[0045] In other embodiments, where the therapeutic agent to be provided includes bioactive drugs, alternate methods of loading onto the loading surface 340 are used. For example, a dip coating, spray, or centrifugation process is used. The dip coating process involves submerging the stent 200 in a solvent having an anti-coagulant or other drug solution. Heparin or heparin coating substances such as Duraflo®, available from Baxter International, Inc., are used as part of the drug solution.

[0046] The stent 200 is then placed into a centrifugation chamber and spun to direct the first solution to particular portions of the stent 200. The stent 200 is then dried and

submerged in a second drug solution. This second drug solution also contains radioactive ions as additional therapeutic agent.

[0047] Mechanical rinsing of the stent 200 is used to remove any excess of the drug solution. Centrifugation of the stent 200 is then repeated to remove excess drug solution.

[0048] In one embodiment, where a volume is provided by increased size indentations 435, drug solution is deposited therein as a result of such methods of loading described above. In other embodiments, such methods of loading are repeated to add bioactive elutable drugs or even a separate anti-coagulant barrier to encase drug solution on the loading surface 340. The barrier is added by dipping, centrifugation and plasma deposition as indicated, or alternately by spraying or plasma polymerization.

[0049] The variability in surface area provided by any combination of the above referenced features accommodating a therapeutic agent allows delivery of therapeutic agent in a manner not limited solely to strut 280 and window cell 290 distribution. As a result, stent 200 embodiments are provided which increase therapeutic agent focus in particular areas of the stent 200.

[0050] In an embodiment of the invention, increased surface area is provided in areas of the stent 200 known to deliver an under-dose of therapeutic agent. Alternatively in another embodiment, less surface area is present in areas known to deliver an overdose of therapeutic agent. These surface area configurations are used to help avoid irregularities or significant variation in delivery of therapeutic agent.

[0051] Additionally, in an embodiment of the invention, increased surface area struts 280 are developed to focus an increased amount of therapeutic agent near stent ends 250, 260. This embodiment helps avoid delivery of sub-threshold levels of

radiation to portions of a vessel immediately adjacent stent ends 250, 260 (i.e. to avoid delivery of between about 2 and about 10 Grays, as measured at 1mm of tissue depth to the vessel 2 in this area). Likewise, another similar embodiment helps provide other therapeutic agents to help combat edge restenosis in this manner. Alternatively, variability in surface area can be used to minimize delivery of a radioactive therapeutic agent near stent ends 250, 260 in order to avoid sub-threshold radiation delivery and edge restenosis.

[0052] Figs. 6-9 show the results of making use of particular variable surface area stent embodiments having unique focuses of therapeutic agent distribution. The results are shown with respect to dose delivery and source profiles.

[0053] For example, Fig. 6 depicts a chart indicating the distribution of therapeutic agent, in the form of radioisotopes, with respect to dose delivery for an embodiment of the invention. The x-axis, labeled "Vessel Length", includes the stent length 601 along with the treatment portion 620 of a vessel. The y-axis, labeled "Dose Delivery (Gy)", indicates the amount of radiation absorbed in Grays (Gy) throughout a vessel 2 such as that of Fig. 1 (as measured from 1 mm of vessel depth).

[0054] Similarly, Fig. 7 represents a source profile of a stent 700 according to the therapeutic distribution indicated in the embodiment of Fig. 6. The profile includes an extension of radioactivity 730 significantly beyond stent ends 750, 760 (ie. hot ends) to help avoid edge restenosis. Also, a uniform field of radioactivity 755 throughout the stent body 751 is provided.

[0055] With reference to the embodiments represented in Figs. 6 and 7, an increased amount of therapeutic agent is provided near stent ends 750, 760 due to the increased loading surface provided thereat. Therefore, where the therapeutic agent is radiation, as with the embodiments of Figs. 6 and 7, delivery of a sub-threshold level of

radiation is avoided at vessel portions immediately adjacent the stent 700 (i.e. within about 2mm of the stent longitudinally).

[0056] Additionally, the stent 700 is configured with increased loading surface directed toward portions of the stent 700 previously responsible for a more uneven distribution of therapeutic agent. In the case of radiation delivery, a more uniform field of radioactivity 755 provides a more consistent delivery of therapeutic agent (i.e. radiation) throughout the stent body 751 of the stent 700.

[0057] A prior art distribution of radiation 51 is un-even. That is, the uniform surface area of a prior art stent may deliver a highly variable dose within a stent length 601. For example, the variable dose can include a maximum dose 91 that is 20 Gy greater than a minimum dose 92 while delivering only an average dose of 20 Gy (with all measurements taken at 1 mm of tissue depth). Alternatively, a more level delivery of radioactivity 650 is provided in embodiments of the invention. Embodiments of the invention can also include peak deliveries of radioactivity 630 to ensure avoidance of sub-threshold delivery 21 in vessel areas of concern, within about 2mm of the stent longitudinally.

[0058] Referring to Figs. 8 and 9, and continuing with the example of a radioactive therapeutic agent, a decreased amount of radioactivity (i.e. an early termination of radioactivity 930) is provided near stent ends in another embodiment of the invention. This is due to the decreased loading surface provided at the stent ends 950, 960 as compared to the remainder of the stent 900. Delivery of a sub-threshold level of radiation is nevertheless minimized or avoided at portions of a vessel immediately adjacent the stent 900 (i.e. within about 2mm of the stent ends 950, 960). That is, any radiation delivered here is below a sub-threshold level to help avoid edge restenosis.

[0059] Additionally, as with Fig. 6, the stent 900 represented by Fig. 9 has been configured to have increased surface area directed toward portions of a stent 900 that would otherwise be responsible for an uneven distribution of therapeutic agent. A more uniform field of radioactivity 955 provides a more consistent delivery of therapeutic agent (i.e. radiation) throughout a stent body of the stent 900 as seen above the x-axis throughout stent length 860.

[0060] Again, by way of comparison, a prior art distribution of radiation 51 is uneven and a sub-threshold level of radiation 21 is delivered by a prior art stent to vessel areas within 2mm of the stent. Alternatively, a more level delivery of radioactivity 850 is provided in embodiments of the invention. Embodiments of the invention can also include tapered deliveries of radioactivity 830 to ensure avoidance of sub-threshold delivery 21 in vessel areas of concern.

[0061] Embodiments of the invention described above include a therapeutic stent which is able to provide an overall pattern of therapeutic agent, where the pattern is not determined solely by strut and window cell distribution throughout the stent. Embodiments of the invention also include patterns of therapeutic agent which help avoid edge restenosis while also helping to avoid delivery of a non-uniform level of therapeutic agent throughout the portion of a vessel to be treated. While such exemplary embodiments have been shown and described in the form of particular stents having variable surface area, many changes, modifications, and substitutions may be made without departing from the spirit and scope of this invention.

CLAIMS

We Claim:

- 1 1. A stent having a variable stent surface area per unit length to accommodate a
2 patterned distribution of a therapeutic agent.
- 1 2. The stent of claim 1 wherein said therapeutic agent is selected from a group
2 consisting of a bioactive drug and a radiation source.
- 1 3. The stent of claim 1 wherein said therapeutic agent is a radiation source, said
2 variable stent surface area configured to avoid delivery of a sub-threshold level of
3 radiation to a vessel wall when said stent is placed adjacent thereto.
- 1 4. The stent of claim 1 wherein said variable stent surface area is configured to
2 reduce variability in delivery of said therapeutic agent to a portion of a vessel adjacent
3 a stent body of said stent.
- 1 5. The stent of claim 1 further comprising struts having a roughened portion with a
2 roughness factor above 1 to provide said variable stent surface area.
- 1 6. The stent of claim 5 wherein said roughened portion is provided by a method of
2 etching a portion of said struts.

1 7. The stent of claim 5 further comprising:
2 a loading surface at an exterior portion of said stent to accommodate said
3 therapeutic agent; and
4 an interior portion of said stent void of said roughened portion.

1 8. The stent of claim 1 further comprising struts having a thickened portion to
2 provide said variable stent surface area.

1 9. The stent of claim 8 wherein said thickened portion is provided by an increased
2 radius portion.

1 10. The stent of claim 8 further comprising increased size indentations having a
2 depth beyond about 80 micrometers to provide said variable stent surface area.

1 11. The stent of claim 10 wherein said thickened portion is provided by cutting a
2 stent pattern from a tube, said stent pattern indicating said thickened portion.

1 12. The stent of claim 11 wherein said cutting is performed by an automated laser
2 method.

3 13. A stent comprising:
4 an end;
5 a variable stent surface area per unit length to accommodate a patterned
6 distribution of a therapeutic agent; and
7 a decreased level of said therapeutic agent at said end.

1 14. A stent comprising:
2 an end;
3 a variable stent surface area per unit length to accommodate a patterned
4 distribution of a therapeutic agent; and
5 an increased level of said therapeutic agent at said end.

1 15. A method of manufacturing a stent for treatment of a vessel, said method
2 comprising:
3 providing a stent with a variable stent surface area per unit length; and
4 disposing a therapeutic agent on said variable stent surface area, said variable
5 stent surface area to allow a patterned distribution of said therapeutic agent throughout
6 said stent.

1 16. The method of claim 15 wherein said providing is achieved by a method of
2 etching selected from a group consisting of chemical etching, plasma etching and laser
3 etching.

1 17. The method of claim 15 wherein said providing is achieved by a lithography
2 technique comprising:
3 covering said stent with a protective polymer;
4 removing a portion of said protective polymer from a selected portion of said
5 stent; and
6 etching a portion of said stent at said selected portion to provide increased
7 roughness thereat.

1 18. The method of claim 17 wherein said protective polymer is ethylene vinyl
2 alcohol.

1 19. The method of claim 17 wherein said selected portion is a stent end.

1 20. The method of claim 17 wherein said etching is performed by a method selected
2 from a group consisting of dry etching with a sand blast and plasma etching with argon.

1 21. A method of manufacturing a stent for treatment of a vessel, said method
2 comprising:

3 providing a stent with a variable stent surface area per unit length;
4 cutting indentations into an exterior surface of said stent, said indentations
5 having a depth beyond about 80 micrometers; and
6 disposing a therapeutic agent on said variable stent surface area, said variable
7 stent surface area allowing a patterned distribution of said therapeutic agent throughout
8 said stent.

1 22. The method of claim 21 wherein said therapeutic agent is a radioactive source,
2 said disposing performed by a method selected from a group consisting of plasma
3 deposition and ion-beam assisted deposition.

1 23. The method of claim 21 wherein said therapeutic agent is a bioactive drug, said
2 disposing performed by a method selected from a group consisting of dip coating,
3 spray, and centrifugation.

1 24. The method of claim 21 wherein said loading includes filling a portion of said
2 indentation with said therapeutic agent.

1 25. The method of claim 21 further comprising adding a protective barrier over said
2 stent after said disposing, said adding performed by a method selected from a group
3 consisting of dip coating, centrifugation, plasma deposition, spraying, and plasma
4 polymerization.

1 26. A method of manufacturing a stent for treatment of a vessel, said method
2 comprising:

3 cutting struts of a stent to have portions of increased thickness providing a stent
4 with a variable stent surface area per unit length; and
5 disposing a therapeutic agent on said variable stent surface area to allow a
6 patterned distribution of said therapeutic agent throughout said stent.

1/4

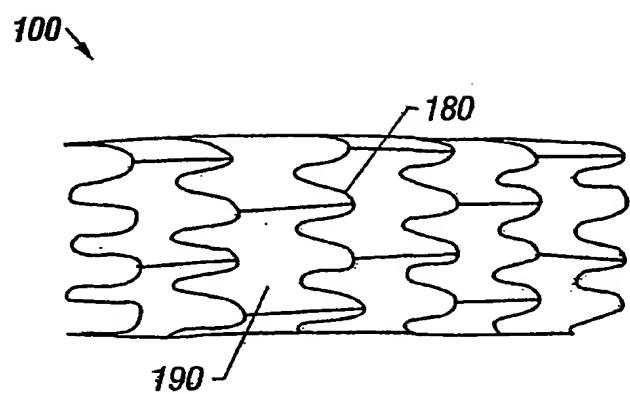


FIG. 1

2/4

200

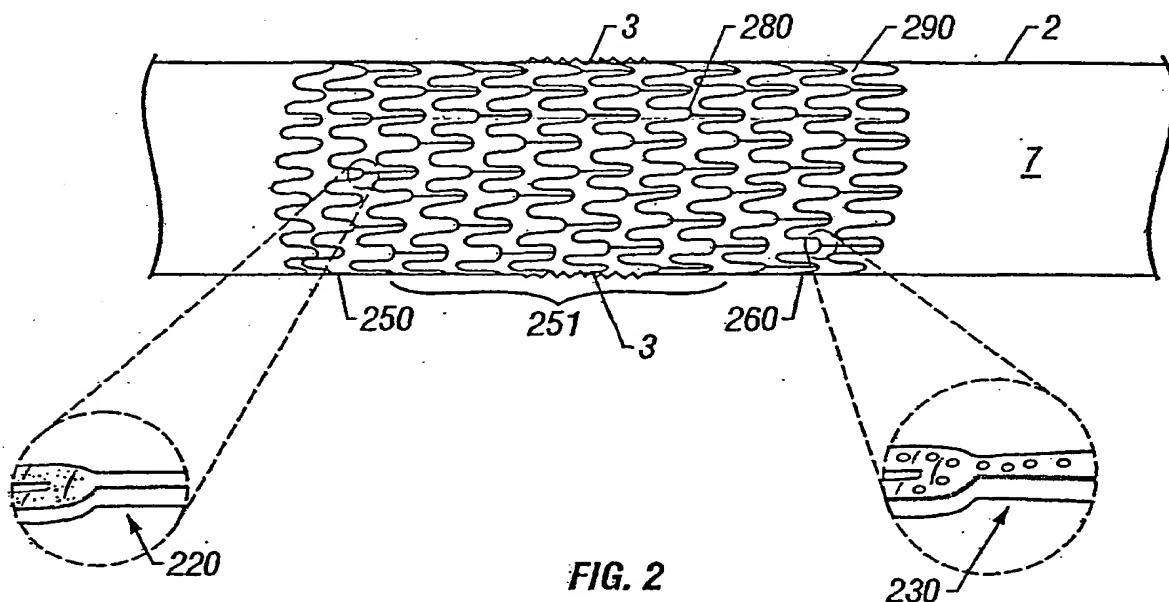


FIG. 2

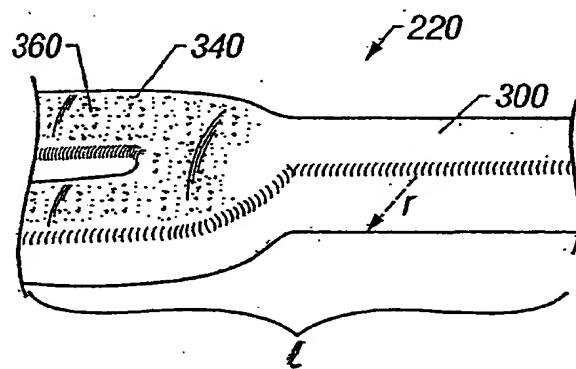


FIG. 3

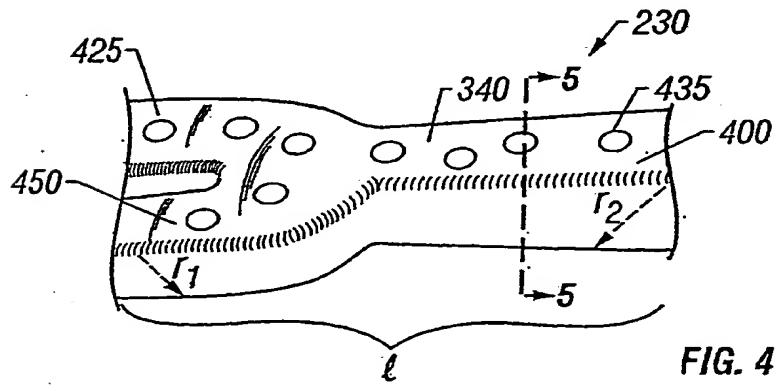


FIG. 4

3/4

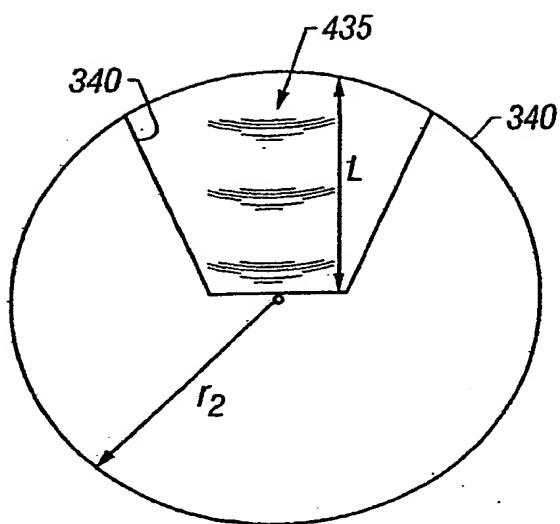


FIG. 5

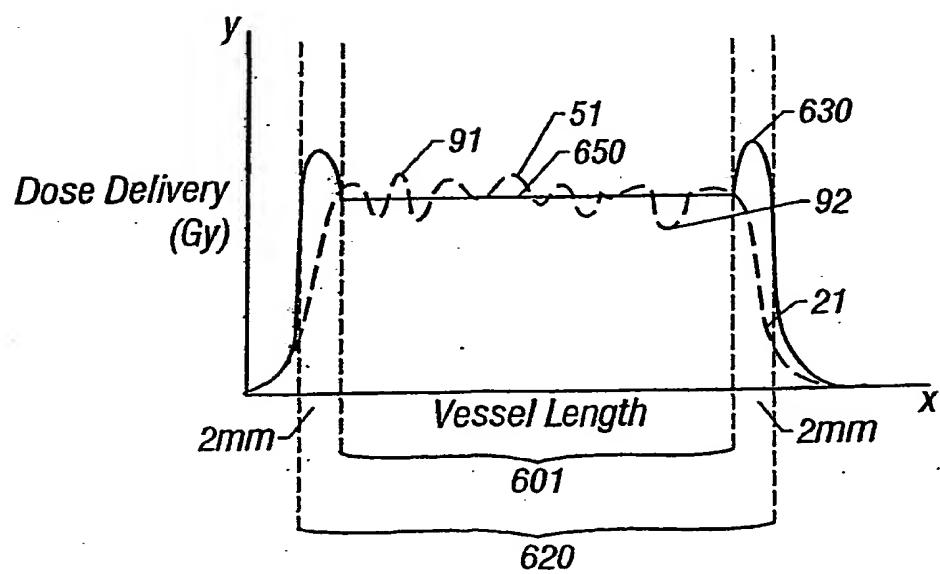


FIG. 6

4/4

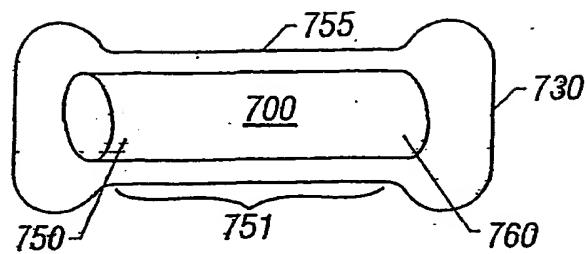


FIG. 7

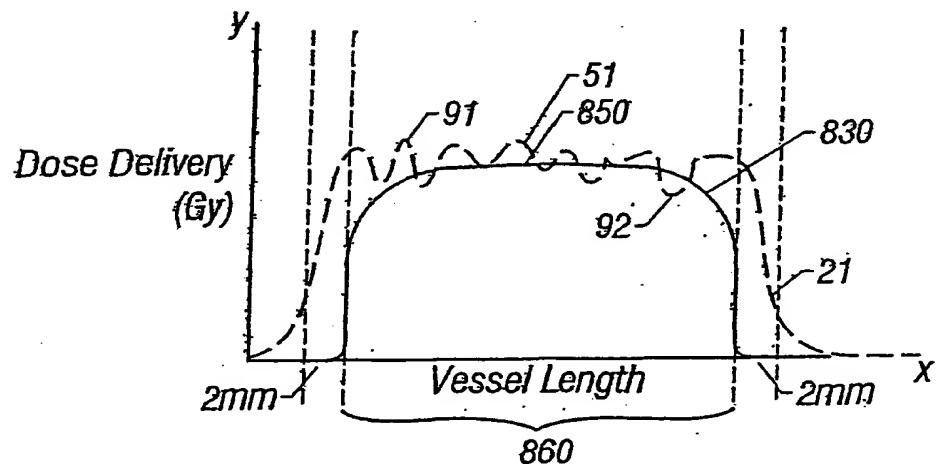


FIG. 8

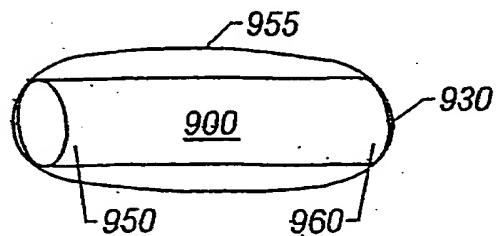


FIG. 9

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/11581

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61F2/06</p> <p>According to International Patent Classification (IPC) or to both national classification and IPC</p>																							
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols)</p> <p>IPC 7 A61F</p>																							
<p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p>																							
<p>Electronic data base consulted during the international search (name of data base and, where practical, search terms used)</p> <p>EPO-Internal</p>																							
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>EP 0 850 604 A (SORIN BIOMEDICA SPA) 1 July 1998 (1998-07-01) column 3, line 21 - line 30 column 3, line 43 -column 6, line 15 claims 1-29</td> <td>1,4-9, 15,16,26</td> </tr> <tr> <td>A</td> <td>—</td> <td>10-14, 17,21-25</td> </tr> <tr> <td>X</td> <td>EP 0 972 498 A (FISCHELL ROBERT ;FISCHELL TIM A (US); FISCHELL DAVID R (US)) 19 January 2000 (2000-01-19) paragraph '0008! - paragraph '0011! claim 1</td> <td>1-3,14, 15,26</td> </tr> <tr> <td>A</td> <td>—</td> <td>13,21</td> </tr> <tr> <td>P,X</td> <td>EP 1 103 234 A (SORIN BIOMEDICA CARDIO SPA) 30 May 2001 (2001-05-30) paragraph '0058! - paragraph '0066! paragraph '0072! - paragraph '0073!</td> <td>1-4,8, 13-16,26</td> </tr> <tr> <td></td> <td>—/—</td> <td></td> </tr> </tbody> </table>			Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	EP 0 850 604 A (SORIN BIOMEDICA SPA) 1 July 1998 (1998-07-01) column 3, line 21 - line 30 column 3, line 43 -column 6, line 15 claims 1-29	1,4-9, 15,16,26	A	—	10-14, 17,21-25	X	EP 0 972 498 A (FISCHELL ROBERT ;FISCHELL TIM A (US); FISCHELL DAVID R (US)) 19 January 2000 (2000-01-19) paragraph '0008! - paragraph '0011! claim 1	1-3,14, 15,26	A	—	13,21	P,X	EP 1 103 234 A (SORIN BIOMEDICA CARDIO SPA) 30 May 2001 (2001-05-30) paragraph '0058! - paragraph '0066! paragraph '0072! - paragraph '0073!	1-4,8, 13-16,26		—/—	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																					
X	EP 0 850 604 A (SORIN BIOMEDICA SPA) 1 July 1998 (1998-07-01) column 3, line 21 - line 30 column 3, line 43 -column 6, line 15 claims 1-29	1,4-9, 15,16,26																					
A	—	10-14, 17,21-25																					
X	EP 0 972 498 A (FISCHELL ROBERT ;FISCHELL TIM A (US); FISCHELL DAVID R (US)) 19 January 2000 (2000-01-19) paragraph '0008! - paragraph '0011! claim 1	1-3,14, 15,26																					
A	—	13,21																					
P,X	EP 1 103 234 A (SORIN BIOMEDICA CARDIO SPA) 30 May 2001 (2001-05-30) paragraph '0058! - paragraph '0066! paragraph '0072! - paragraph '0073!	1-4,8, 13-16,26																					
	—/—																						
<p><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</p>																							
<p><input checked="" type="checkbox"/> Patent family members are listed in annex.</p>																							
<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>																							
<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>																							
<p>Date of the actual completion of the international search</p> <p>12 August 2002</p>		<p>Date of mailing of the international search report</p> <p>22/08/2002</p>																					
<p>Name and mailing address of the ISA</p> <p>European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016</p>		<p>Authorized officer</p> <p>Mary, C</p>																					

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/11581

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 199 16 086 A (INFLOW DYNAMICS INC) 14 October 1999 (1999-10-14) column 4, line 60 -column 6, line 29	1-26
A	EP 0 701 803 A (AO FORSCHUNGSGINST) 20 March 1996 (1996-03-20) column 3, line 42 - line 49 claim 1	1-26
A	US 5 826 586 A (MISHRA AJIT K ET AL) 27 October 1998 (1998-10-27) column 4, line 40 - line 48 claim 1	15-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/11581

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
EP 0850604	A	01-07-1998	IT EP EP	T0961095 A1 1181903 A2 0850604 A2	30-06-1998 27-02-2002 01-07-1998
EP 0972498	A	19-01-2000	US EP TW	5840009 A 0972498 A1 386035 B	24-11-1998 19-01-2000 01-04-2000
EP 1103234	A	30-05-2001	EP	1103234 A1	30-05-2001
DE 19916086	A	14-10-1999	US DE US US WO	5980566 A 19916086 A1 6099561 A 6387121 B1 9952471 A1	09-11-1999 14-10-1999 08-08-2000 14-05-2002 21-10-1999
EP 0701803	A	20-03-1996	DE DE EP ES	69512593 D1 69512593 T2 0701803 A1 2138094 T3	11-11-1999 20-01-2000 20-03-1996 01-01-2000
US 5826586	A	27-10-1998	AU WO	5095196 A 9629030 A1	08-10-1996 26-09-1996

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER: _____**

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.